

TISSUE CHARACTERIZATION BASED ON IMPEDANCE IMAGES  
AND ON IMPEDANCE MEASUREMENTS

CROSS REFERENCE TO RELATED APPLICATION

This application is a Continuation-in-Part of International Application No. PCT/US95/06141, filed May 19, 1995, the disclosure of which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to systems for tissue characterization based on impedance measurement at a point or at an array of points.

BACKGROUND OF THE INVENTION

The measurement of electrical potentials on the skin has many uses. For example, electrocardiograms are derived from measuring the potential generated by the heart of a patient at various points on the skin.

Skin potentials are also measured in apparatus for determining the electrical impedance of human tissue, including two-dimensional (e.g., U.S. Patents 5,063,937, 4,291,708 and 4,458,694) or three-dimensional (e.g., U.S. Patents 4,617,939 and 4,539,640) mapping of the tissue impedance of the body. In such systems an electrical potential is introduced at a point or points on the body and measured at other points at the body. Based on these measurements and on algorithms which have been developed over the past several decades, an impedance map or other indication of variations in impedance can be generated.

U.S. Patents 4,291,708 and 4,458,694 and "Breast Cancer screening by impedance measurements" by G. Piperno et al. Frontiers Med. Biol. Eng., Vol. 2, pp 111-117, the disclosures of which are incorporated herein by reference, describe systems in which the impedance between a point on the surface of the skin and some reference point on the body of a patient is determined. These references describe the use of a multi-element probe for the detection of cancer, especially breast cancer, utilizing detected variations of impedance in the breast.

In these references a multi-element probe is described in which a series of flat, stainless steel, sensing elements are mounted onto a PVC base. A lead wire is connected between each of these elements and detector circuitry. Based on the impedance measured between the elements and a remote part of the body, signal processing circuitry determines the impedance variations in the breast. Based on the impedance

1 determination, tumors, and especially malignant tumors, can  
2 be detected.

3       The multi-element probe is a critical component in this  
4 system and in other systems which use such probes. On one  
5 hand the individual elements must make good contact with the  
6 skin and with the corresponding points on the sensing or  
7 processing electronics while also being well isolated from  
8 each other. On the other hand, use of gels to improve skin  
9 contact carries the risk of cross-talk, dried gel build-up on  
10 the elements and inter-patient hygienic concerns.

11       A paper titled "Capacitive Sensors for In-Vivo  
12 Measurements of the Dielectric Properties of Biological  
13 materials" by Karunayake P.A.P. Esselle and Stanislaw S.  
14 Stuchly (IEEE Trans. Inst & Meas. Vol. 37, No. 1, p. 101-105)  
15 describes a single element probe for the measurement of in  
16 vivo and in vitro measurements of the dielectric properties  
17 of biological substances at radio and microwave frequencies.  
18 The sensor which is described is not suitable for impedance  
19 imaging.

20       A paper entitled "Messung der elektrischen Impedance von  
21 Organen- Apparative Ausrüstung für Forschung und klinische  
22 Anwendung" by E. Gersing (Biomed. Technik 36 (1991), 6-11)  
23 describes a system which uses single element impedance probes  
24 for the measurement of the impedance of an organ. The device  
25 described is not suitable for impedance imaging.

26       A Paper titled "MESURE DE L'IMPEDANCE DES TISSUS  
27 HEPATIQUELES TRANSFORMES PAS DES PROCESSUS LESIONELS" by J.  
28 Vrana et al. (Ann. Gastroentreol. Hepetol., 1992, 28, no. 4,  
29 165-168) describes a probe for assessing deep tissue by use  
30 of a thin injection electrode. The electrode was positioned  
31 by ultrasound and specimens were taken for cytological and  
32 histological assessment. The electrode was constituted on a  
33 biopsy needle used to take the samples.

34       A paper titled "Continuous impedance monitoring during  
35 CT-guided stereotactic surgery: relative value in cystic and  
36 solid lesions" by V. Rajshekhar (British Journal of  
37 Neurosurgery (1992) 6, 439-444) describes using an impedance  
38 probe having a single electrode to measure the impedance  
39 characteristics of lesions. The objective of the study was to

1 use the measurements made in the lesions to determine the  
2 extent of the lesions and to localize the lesions more  
3 accurately. The probe is guided to the tumor by CT and four  
4 measurements were made within the lesion as the probe passed  
5 through the lesion. A biopsy of the lesion was performed  
6 using the outer sheath of the probe as a guide to position,  
7 after the probe itself was withdrawn.

8 A paper titled "Rigid and Flexible Thin-Film Multi-  
9 electrode Arrays for Transmural Cardiac Recording" by J. J.  
10 Mastrototaro et al. (IEEE TRANS. BIOMED. ENG. Vol. 39, No. 3,  
11 March 1992, 271-279) describes a needle probe and a flat  
12 probe each having a plurality of electrodes for the  
13 measurement of electrical signals generated in the heart.

14 A paper entitled "Image-Based Display of Activation  
15 Patterns Derived from Scattered Electrodes" by D. S. Buckles  
16 et al. (IEEE TRANS. BIOMED ENGR. Vol. 42, No. 1, January  
17 1995, 111-115) describes a system for measurement of  
18 electrical signals generated on the heart by use of an array  
19 of electrodes on a substrate. The heart with the electrodes  
20 in place is viewed by a TV camera and an operator marks the  
21 positions of the electrodes on a display. The system then  
22 displays the heart (as visualized prior to the placement of  
23 the electrodes) with the position markings.

24 A paper entitled "Development of a Multiple Thin-Film  
25 Semimicro DC-Probe for Intracerebral Recordings" by G. A.  
26 Urban et al. (IEEE TRANS. BIOMED ENGR. Vol. 37, No. 10,  
27 October 1990, 913-917) describes an elongate alumina ceramic  
28 probe having a series of electrodes along its length and  
29 circumference for measuring functional parameters (electrical  
30 signals) in the brain. Electrophysiological recording,  
31 together with electrostimulation at the target point during  
32 stereotactic surgery, was performed in order to ensure exact  
33 positioning of the probe after stereotactic calculation of  
34 the target point. Bidimensional X-Ray imaging was used in  
35 order to verify the exact positioning of the electrode tip.

#### 36 SUMMARY OF THE INVENTION

37 It is an object of certain aspects of the invention to  
38 provide a multi-element probe having improved and more  
39 uniform and repeatable contact with the skin with minimal

1 operator expertise and minimal risk of cross-patient  
2 contamination.

3 It is an object of certain aspects of the invention to  
4 provide improved inter-element electrical isolation, and to  
5 permit sliding of the probe while it is urged against the  
6 skin.

7 It is an object of certain aspects of the invention to  
8 provide a relatively inexpensive disposable multi-element  
9 probe.

10 It is an object of certain aspects of the invention to  
11 provide a multi-element probe having sufficient transparency  
12 to allow for viewing of tissue surface features and to allow  
13 for referencing the probe with respect to physical features  
14 of or on the skin.

15 It is an object of certain aspects of the invention to  
16 provide a method of distinguishing between artifacts and  
17 abnormalities.

18 It is an object of certain aspects of the invention to  
19 provide a system for electrical impedance imaging which  
20 simultaneously acquires, uses and preferably displays both  
21 capacitance and conductance information.

22 It is an object of certain aspects of the invention to  
23 provide a system for electrical impedance testing of the  
24 breast or other body region which provides more accurate  
25 information regarding the position of impedance abnormalities  
26 detected in the breast or other region.

27 It is an object of certain aspects of the invention to  
28 provide for electrical impedance testing with a variable  
29 spatial resolution.

30 It is an object of certain aspects of the invention to  
31 provide for two dimensional electrical impedance testing  
32 giving an indication of the distance of an abnormality from  
33 the surface of the skin.

34 It is an object of certain aspects of the invention to  
35 provide apparatus especially suitable for breast impedance  
36 measurements.

37 It is an object of certain aspects of the invention to  
38 provide guidance for placement of elongate objects such as  
39 biopsy needles, localization needles, fiber optic endoscopes

1 and the like using real time and/or recorded stereotactic  
2 images to guide the object.

3 It is a further object of certain aspects of the  
4 invention to provide a biopsy needle having an impedance  
5 measuring function to aid in the taking of a biopsy.

6 It is an object of certain aspects of the invention to  
7 provide more direct comparison between the results of  
8 electrical impedance maps and the results of optical,  
9 ultrasound or other imaging modalities.

10 It is an object of certain aspects of the invention to  
11 provide apparatus and method for indicating, on an anatomical  
12 illustration, the location and region from which an impedance  
13 image, shown together with the illustration is derived.

14 It is an object of certain aspects of the invention to  
15 provide apparatus which facilitates direct comparison between  
16 X-Ray and impedance mammographic images, as for example by  
17 superposition of the images.

18 It is an object of certain aspects of the invention to  
19 provide a method of determining a polychromic (multi-  
20 frequency) impedance map.

21 It is an object of certain aspects of the invention to  
22 optimize the impedance mapping utilizing a pulsed voltage  
23 excitation.

24 It is an object of certain aspects of the invention to  
25 provide palpation and tactile sensing of an area while  
26 simultaneously providing an impedance image of the area.

27 It is an object of certain aspects of the invention to  
28 allow for the identification of tissue types from impedance  
29 maps.

30 In general, the term "skin" as used herein means the  
31 skin or other tissue of a subject.

32 The present inventor has found that when, in an  
33 impedance image, an anomaly is perceived, the type of tissue  
34 underlying the position of the anomaly on the image may  
35 generally be determined by a characterization procedure which  
36 includes the determination of a number of polychromic  
37 measures for the anomaly and surrounding non-anomalous tissue  
38 and comparison of the measures with ranges of values of  
39 individual polychromic measures or their combinations which

1 are characteristic of various types of tissue. It has been  
2 found that normal tissue such as breast tissue, nipples and  
3 the infra-mammary ridge, ribs and Costo-chondral Junctions  
4 and benign hyperplasia can generally be distinguished from  
5 cancerous tumors and precancerous atypical hyperplasia. These  
6 measures are based on the structure and form of the deviation  
7 of the capacitance and conductance of the anomalous portion  
8 of the image from that of the surrounding, normal tissue. For  
9 those cases where there is some ambiguity between some types  
10 of tissue, knowledge of the anatomy of the imaged area or  
11 palpation of the area can often remove the ambiguity or  
12 additional views can be taken to remove the ambiguity.

13 In an image the measures are preferably determined by  
14 comparing the capacitance or conductance of the anomalous  
15 pixels on the image to be characterized with the capacitance  
16 or conductance of normative tissue around the mean or median  
17 value of the capacitance or conductance, typically in terms  
18 of quantified deviation of a given pixel or region from the  
19 median in the image, as measured in multiples of the  
20 estimated standard deviation or coefficient of variance.

21 The method is also potentially useful to determine  
22 tissue types in situations where either a single impedance  
23 probe is used or where the image is small and only anomalous  
24 areas are imaged. In these cases the comparison is made  
25 between the values of capacitance or conductance measured for  
26 the anomalous region as compared to the capacitance or  
27 conductance measured for a nearby region known to be normal.

28 As used herein the term immittance means either the  
29 complex admittance or impedance. Furthermore the term  
30 polychromic measure is a measure which is based on the  
31 immittance or on the real or imaginary part thereof or on a  
32 combination of the immittance and/or the real part thereof  
33 and/or the imaginary part thereof at a plurality of  
34 frequencies, i.e., on the spectrum thereof.

35 There is therefore provided, in accordance with a  
36 preferred embodiment of the invention apparatus for aiding in  
37 the identification of tissue type for an anomalous tissue in  
38 an impedance image comprising:

39 means for providing an polychromic immittance map of a

1 portion of the body;

2 means for determining a plurality of polychromatic  
3 measures, preferably normalized measures, of an anomalous  
4 region of the immitance image; and

5 a display which displays an indication based on said  
6 plurality of polychromatic measures.

7 Preferably the apparatus includes means for providing a  
8 map of said polychromatic measures and wherein said indication  
9 includes a display of a plurality of said maps.

10 In a preferred embodiment of the invention the display  
11 includes an overlay of maps of said polychromatic measures.

12 Preferably the apparatus includes means for matching the  
13 values of the plurality of measures with predetermined values  
14 of the measures to identify the tissue type of the anomalous  
15 tissue.

16 In one preferred embodiment of the invention the  
17 indication is the display of a map of said determined tissue  
18 type.

19 There is further provided, in accordance with a  
20 preferred embodiment of the invention, apparatus for  
21 determining a tissue type for an anomalous tissue comprising:

22 means for determining a plurality of polychromatic  
23 measures of the anomalous tissue; and

24 means for matching the values of the plurality of  
25 measures with predetermined values of the measures to  
26 identify the tissue type of the anomalous tissue.

27 There is further provided, in accordance with a  
28 preferred embodiment of the invention, a method of  
29 determining a tissue type for tissue in an anomalous region  
30 in an immitance image, comprising:

31 determining a plurality of polychromatic measures,  
32 preferably normalized measures, of said anomalous region; and

33 matching the values of the plurality of measures to  
34 identify the tissue type of the anomalous region.

35 There is further provided, in accordance with a  
36 preferred embodiment of the invention, a method of  
37 determining a tissue type for an anomalous tissue:

38 determining a plurality of polychromatic measures,  
39 preferably normalized measures, of the anomalous tissue;



1 matching the values of the plurality of measures with  
2 predetermined values to identify the tissue type of the  
3 anomalous tissue.

4 Preferably, one of the polychromic measures is derived  
5 from the sum, over a plurality of frequencies, of the  
6 positive deviations of the capacitance of the anomaly from  
7 that of typical nonanomalous regions.

8 Preferably, one of the polychromic measures is derived  
9 from the sum, over a plurality of frequencies, of the  
10 negative deviations of the capacitance of the anomaly from  
11 that of typical nonanomalous regions.

12 Preferably, one of the polychromic measures is derived  
13 from the sum, over a plurality of frequencies, of the  
14 positive deviations of the conductance of the anomaly from  
15 that of typical nonanomalous regions.

16 Preferably one of the measures is the integral of the  
17 phase or the sum of phase values over a range of frequencies.

18 Preferably, one of the measures is the difference  
19 between the integral of the difference between the phase at a  
20 point and the mean or median value of the phase in the image,  
21 over a range of frequencies.

22 Preferably, one of the measures is the derivative of the  
23 capacitance curve or its logarithm as a function of  
24 frequency, evaluated at a given frequency.

25 Preferably, one of the measures is the derivative of the  
26 conductance curve or its logarithm as a function of  
27 frequency, evaluated at a given frequency.

28 Preferably, one of the measures is a frequency at which  
29 the phase of the impedance reaches a specified value,  
30 preferably 45 degrees.

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BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be more fully understood and appreciated from the following detailed description, taken in conjunction with the drawings in which:

Fig. 1 is an overall view of an impedance mapping system especially suitable for breast impedance mapping in accordance with a preferred embodiment of the invention;

Fig. 2 is a perspective view of an imaging head suitable for breast impedance mapping in accordance with a preferred embodiment of the invention;

Figs. 3A and 3B show partially expanded views of two preferred probe head configurations suitable for use in the imaging head of Fig. 2;

Fig. 4 is a top view of a portion of a multi-element probe in accordance with a preferred embodiment of the invention;

Fig. 5A is a partial, partially expanded cross-sectional side view of the probe of Fig. 4 along lines V-V, suitable for the probe head configuration of Fig. 3B;

Fig. 5B is a partially expanded cross-sectional side view of an alternative probe in accordance with a preferred embodiment of the invention;

Fig. 5C shows an alternative embodiment of a multi-element probe, in accordance with a preferred embodiment of the invention;

Fig. 6A is a perspective view of a hand held probe in accordance with a preferred embodiment of the invention;

Fig. 6B shows a partially expanded bottom view of the probe of Fig. 6A, in accordance with a preferred embodiment of the invention;

Fig. 7A is a perspective view of a fingertip probe in accordance with a preferred embodiment of the invention;

Fig. 7B shows a conformal multi-element probe;

Fig. 8 shows an intra-operative probe used determining the position of an abnormality in accordance with a preferred embodiment of the invention;

Fig. 9 shows a laparoscopic probe in accordance with a preferred embodiment of the invention;

Fig. 10 shows a biopsy needle in accordance with a

1 preferred embodiment of the invention;

2 Fig. 11A illustrates a method of using the biopsy needle  
3 of Fig. 10, in accordance with a preferred embodiment of the  
4 invention;

5 Fig. 11B illustrates a portion of a display used in  
6 conjunction with the method of Fig. 11A;

7 Fig. 11C shows a biopsy guiding system in accordance  
8 with a preferred embodiment of the invention;

9 Fig. 11D shows a frontal biopsy guiding system in  
10 accordance with a preferred embodiment of the invention;

11 Fig. 11E shows a lateral biopsy guiding system in  
12 accordance with a preferred embodiment of the invention;

13 Fig. 12 shows, very schematically, the inter-operative  
14 probe of Fig. 8 combined with a video camera use to more  
15 effectively correlate an impedance measurement with placement  
16 of the probe.

17 Fig. 13 illustrates a laparoscopic probe according to  
18 the invention used in conjunction with a fiber-optic  
19 illuminator-imager;

20 Fig. 14 illustrates a display, according to a preferred  
21 embodiment of the invention showing both capacitive and  
22 conductance images illustrative of atypical hyperplasia;

23 Fig. 15 illustrates a display, according to a preferred  
24 embodiment of the invention showing both capacitive and  
25 conductance images illustrative of a carcinoma;

26 Fig. 16 illustrates a method useful for verifying a  
27 detected local impedance deviation as being non-artifactual  
28 and for estimating the deviation;

29 Figs. 17A and 17B are a block diagram of circuitry  
30 suitable for impedance mapping in accordance with a preferred  
31 embodiment of the invention; and

32 Figs. 18A-18C show maps of polychromic measures  
33 characteristic of certain tissue types.

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1           DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

2           Reference is made to Figs. 1 and 2 which illustrate an  
3 impedance mapping device 10 suitable for mapping the  
4 impedance of a breast.

5           Mapping device 10 includes an imaging head 12, which is  
6 described below, which holds the breast and provides contact  
7 therewith for providing electrical excitation signals thereto  
8 and for receiving resultant electrical signals therefrom.

9           Signals to and from the head are generated and received by a  
10 computer/controller 14 which produces impedance maps of the  
11 breast under test for display on a monitor 16. The impedance  
12 maps may be stored in computer/controller 14 for later  
13 viewing or processing or hard copies may be provided by a  
14 hard copy device 18 which may be a laser printer, video  
15 printer, Polaroid or film imager or multi-imager.

16           The entire mapping device 10 may be conveniently mounted  
17 on a dolly 20 to facilitate placement of the imaging head  
18 with respect to the patient.

19           Fig. 1 also shows a hand held probe 100, described in  
20 more detail below, and a reference probe 13.

21           Fig. 2 shows imaging head 12 in more detail. Head 12  
22 comprises a movable lower plate probe 22 and a stationary  
23 upper plate probe 24 which is mounted on a pair of rails 26  
24 to allow the distance between plate probes 22 and 24 to be  
25 varied.

26           Movement of plate probe 22 along rails 26 may be  
27 achieved either by a motor (not shown) including suitable  
28 protection against over-pressure as is traditional in X-ray  
29 breast imaging, or by hand.

30           Either or both of plate probes 22 and 24 are provided  
31 with multi-element probes 28 and 30 respectively, which are  
32 described more fully below, which electrically contact the  
33 breast with a plurality of sensing elements to optionally  
34 provide electrical excitation to the breast and to measure  
35 signals generated in response to the provided signals.  
36 Alternatively, electrical excitation to the breast is  
37 provided by reference probe 13 which is placed on the arm,  
38 shoulder or back of the patient, or other portion of the  
39 patient.

1 In practice, a breast is inserted between probes 28 and  
2 30 and plate probe 24 is lowered to compress the breast  
3 between the probes. This compression reduces the distance  
4 between the probes and provides better contact between the  
5 sensing elements and the skin of the breast. Although  
6 compression of the breast is desirable, the degree of  
7 compression required for impedance imaging is much lower than  
8 for X-Ray mammography, and the mapping technique of the  
9 present invention is typically not painful.

10 Alternatively or additionally, the probes are curved to  
11 conform with the surface of the breast.

12 Head 12 is provided with a pivot (not shown) to allow  
13 for arbitrary rotation of the head about one or more of its  
14 axes. This allows for both medio-lateral and cranio-caudal  
15 maps of the breast to be acquired, at any angular orientation  
16 about the breast. Preferably, head 12 may be tilted so that  
17 the surfaces of plate probes 22 and 24 are oriented with a  
18 substantial vertical component so that gravity assists the  
19 entry of the breast into the space between the maximum extent  
20 and to keep it from inadvertently falling out. This is  
21 especially useful when the patient leans over the plates so  
22 that her breasts are positioned downwardly between the plate  
23 probes.

24 Furthermore, in a preferred embodiment of the invention,  
25 one or both of probes 28 and 30 may be rotated about an axis  
26 at one end thereof, by a rotation mechanism 27 on their  
27 associated plate probes 22 or 24, such as is shown in Fig. 2  
28 for probe 28. Additionally or alternatively, probes 28 and/or  
29 30 may be slidable, as for example along members 31.

30 Such additional sliding and rotating flexibility is  
31 useful for providing more intimate skin contact of the probes  
32 with the breast, which has a generally conical shape.  
33 Furthermore, such flexibility allows for better imaging of  
34 the areas of the breast near the chest wall or the rib cage,  
35 which are extremely difficult to image in x-ray mammography.

36 Figs. 3A and 3B show partially expanded views of two  
37 probe head configurations suitable for use in the imaging  
38 head of Fig. 2, in accordance with preferred embodiments of  
39 the invention.

1 In the embodiment of Fig. 3A, a preferably removable  
2 multi-element probe 62, which is described below in more  
3 detail, is attached to a probe head base 50 via a pair of  
4 mating multi-pin connectors 51 and 52. A cable 53 couples  
5 connector 52 to computer 14. When multi-element probe 62 is  
6 inserted into base 50 (that is to say, when connector 51 is  
7 fully inserted into connector 52), the relatively stiff  
8 bottom of probe 62 rests on ledges 54 formed in the base,  
9 such that the surface 55 of the base and the surface of  
10 element 62 are preferably substantially coplanar.

11 In the embodiment of Fig. 3B, a series of contacts 82  
12 are formed on base 50 and a disposable multi-element probe  
13 62' is attached to the contacts as described below with  
14 reference to Fig. 5A and 5B. Cable 53 couples the contacts to  
15 computer 14.

16 Figs. 4, 5A and 5B show top and side views of a portion  
17 of multi-element probe 62' and contacts 74, while Figs. 5A  
18 and 5B show a partially expanded cross-sectional side view  
19 of probe 62' along lines V-V. While the embodiment shown in  
20 Figs. 4, 5A and 5B is especially suitable for the probe head  
21 configuration of Fig. 3B, much of the structure shown in  
22 these figures is common to multi-element probes used in  
23 other configurations described herein.

24 As shown in Figs. 4, 5A and 5B, disposable multi-element  
25 probe 62' preferably incorporates a plurality of sensing  
26 elements 64, separated by separator or divider elements 66.

27 As shown more clearly in Figs. 5A and 5B, sensing  
28 elements 64, comprise a bio-compatible conductive material  
29 (for example Neptrode E0751 or Neptrode E0962 Hydrogel  
30 distributed by Cambrex Hydrogels, Harriman, NY) such as is  
31 sometimes used for ECG probes in a well 70 formed by a first,  
32 front, side of a mylar or other flexible, non-conducting  
33 substrate 68, such as a thin mylar sheet and the divider  
34 elements 66. A suitable thickness for the mylar sheet is  
35 approximately 0.2 mm for probe 62'. The substrate is  
36 preferably pierced in the center of each well. The hole  
37 resulting from the piercing is filled with a conducting  
38 material which is also present on the bottom of well 70 and  
39 on a second, back, side of substrate 68 to form a pair of

1 electrical contacts 72 and 74 on either side of the  
2 substrate and an electrically conducting feed-through 76  
3 between the pair of contacts. As shown, a separate contact  
4 pair and feed-through is provided for each sensing element.

5 Alternatively, the substrate may be formed of any  
6 suitable inert material including plastics such as  
7 polyethylene, polypropylene, PVC, etc.

8 Wells 70 may be formed in a number of ways. One method  
9 of forming the wells is to punch an array of square holes in  
10 a sheet of plastic, such as polypropylene, which is about  
11 0.2-1mm thick. This results in a sheet containing only the  
12 divider elements. This sheet is bonded to substrate 68 which  
13 has been pre-pierced and in which the contacts and feed-  
14 throughs have been formed. Another method of forming the  
15 wells is to emboss a substrate containing the contacts and  
16 feed-throughs to form divider elements in the form of ridges  
17 which protrude from the substrate as shown in Fig. 5B. Yet  
18 another method of producing the wells is by printing the well  
19 walls using latex based ink or other bio-compatible material  
20 having a suitable firmness and flexibility. Another method of  
21 production is by injection molding of the substrate together  
22 with the divider elements. And yet another method of  
23 producing the wells is by laminating to the substrate a  
24 preformed grid made by die cutting the array of divider  
25 elements in a sheet of plastic, injection molding, or other  
26 means.

27 The conductors and feed-throughs may be of any  
28 conductive material which will provide reliable feed-through  
29 plating of the holes. One method of manufacturing the  
30 contacts and holes is by screen printing of the contacts on  
31 both sides of the substrate. If conductive paste having a  
32 suitable viscosity is used, the paste will fill the hole and  
33 form a reliable contact between contacts 72 and 74. Although  
34 many conductive materials can be used, non-polarizing  
35 conductors, such as silver/silver chloride are preferred. A  
36 conductive paste suitable for silk screening the conductors  
37 onto the substrate is Pad Printable Electrically conductive  
38 Ink No. 113-37 manufactured and sold by Creative Materials  
39 Inc., Tyngsboro, MA.

1 In general contacts 72 and 74 are only 10-200 microns  
2 thick and wells 70 are generally filled with conductive  
3 viscous gel material or hydrogel material to within about  
4 0.2 mm of the top of the dividing elements. In general, if  
5 low separators are used, the hydrogel may be omitted.  
6 However, in the preferred embodiment of the invention, the  
7 wells are at least partially filled by hydrogel or a similar  
8 material.

9 Hydrogel is available in both UV cured and heat cured  
10 compositions. In either case a measured amount of uncured  
11 semi-liquid hydrogel is introduced into each well and the  
12 hydrogel is cured. Alternatively, the wells are filled with  
13 the uncured material and a squeegee which is pressed against  
14 the top of the divider elements with a predetermined force is  
15 moved across the top of the divider elements. This will  
16 result in the desired gap between the top of the hydrogel and  
17 the top of the wells.

18 In an alternative embodiment of the invention, the  
19 hydrogel material is replaced by a sponge material or similar  
20 supportive matrix impregnated with conductive viscous gel or  
21 the well is simply filled with the conductive gel to the  
22 desired height.

23 During use of the probe, the probe is urged against the  
24 skin which is forced into the wells and contacts the hydrogel  
25 or alternative conductive material. Optionally, a somewhat  
26 viscous conductive gel, such as Lectron II Conductivity Gel  
27 (Pharmaceutical Innovations, Inc. Newark, NJ), may be used to  
28 improve contact with the skin. In this case, the dividing  
29 elements will reduce the conduction between the cells such  
30 that the substantial independence of the individual  
31 measurements is maintained. Alternatively, the conductive gel  
32 may be packaged together with the probe, with the conductive  
33 gel filling the space between the top of the hydrogel and the  
34 top of the wells. The use of a conductive gel is preferred  
35 since this allows for sliding movement of the probe and its  
36 easy positioning while it is urged against the skin. The  
37 separators substantially prevent the conductive gel from  
38 creating a low conductance path between adjoining sensing  
39 elements and also keep the hydrogel elements from touching



1 each other when the probe is applied to the skin with some  
2 pressure.

3 In a further preferred embodiment of the invention, the  
4 sensing elements are formed of a conductive foam or sponge  
5 material such as silicone rubber or other conductive rubber  
6 or other elastomer impregnated with silver or other  
7 conductive material, as shown in Fig. 5C. Fig. 5C shows the  
8 sensing elements without walls 66. Elements which protrude  
9 from the substrate as shown in Fig. 5C may achieve  
10 substantial electrical isolation from one another by spacing  
11 them far enough apart so that do not contact each other in  
12 use or by coating their lateral surfaces with insulating  
13 material such as polyethylene or other soft non-conductive  
14 plastic or rubber.

15 For relatively short rigid or compressible elements, it  
16 has been found that reducing the size of the sensing elements  
17 such that no more than 70% (and preferably no more than 50%)  
18 of the area of the array is covered is sufficient to reduce  
19 the "cross-talk" between adjoining elements to an acceptable  
20 level.

21 If sufficiently good isolation is achieved between probe  
22 elements by their spacing alone, then foam or other elements  
23 without hydrogel and without walls 66 may be provided.  
24 Sensing elements such as those shown in Fig. 5C conform and  
25 mate to uneven surfaces when pressed against tissue.

26 Multi-element probe 62', which is preferably used for  
27 only one patient and then discarded, is preferably removably  
28 attached to a probe holder which preferably comprises a  
29 printed circuit board 80 having a plurality of contacts 82  
30 corresponding to the contacts 74 on the back of the  
31 substrate, each PC board contact 82 being electrically  
32 connected to a corresponding contact 74 on the substrate. To  
33 facilitate alignment of the matching contacts, an alignment  
34 guide 90 is preferably provided on or adjacent to PC board 80  
35 (Fig. 4). This guide may consist of a series of guide marks  
36 or may consist of a raised edge forming a well into or onto  
37 which the substrate is inserted. Conductors within PC board  
38 80 connect each of the contacts to one of the pins of  
39 connector 51, which is preferably mounted on PC board 80.

1       Alternatively and preferably, as described below with  
2       respect to Fig. 6B, the guide may consist of two or more pins  
3       located on or near PC board 80, which fit into matching holes  
4       in probe 62'.

5       Alternatively as shown in Fig. 5B, the back side of the  
6       embossing of substrate 68 is used as the guide for one or  
7       more protruding elements 83 which are preferably mounted on  
8       PC board 80. Preferably a plurality of protruding elements  
9       are provided to give good alignment of the substrate with the  
10      PC board. The elements may run along the periphery of the  
11      probe and form a frame-like structure as shown in Fig. 5B or  
12      may run between the elements or may take the form of x shaped  
13      protuberances which match the shape of the embossing at the  
14      corners of the wells.

15      Protruding elements 83 may be formed of polycarbonate,  
16      acetate, PVC or other common inert plastic, or of a  
17      noncorrosive metal such as stainless steel.

18      A wire 84 is connected to each PC contact 82 and is also  
19      connected to apparatus which provides voltages to and/or  
20      measures voltages and/or impedances at the individual sensing  
21      elements 64, as described below.

22      In a preferred embodiment of the invention, conductive  
23      adhesive spots 86 preferably printed onto the back of the  
24      substrate are used to electrically and mechanically connect  
25      contacts 74 with their respective contacts 82. Preferably a  
26      conductive adhesive such as Pressure Sensitive Conductive  
27      Adhesive Model 102-32 (Creative Materials Inc.) is used.  
28      Alternatively, the adhesive used for printing the  
29      contacts/feed-throughs is a conducting adhesive and adhesive  
30      spots 86 may be omitted. Alternatively, pins, which protrude  
31      from the surface of PC board 80 and are connected to wires 84  
32      pierce the substrate (which may be pre-bored) and contact the  
33      gel or hydrogel in the wells. A pin extending from the  
34      substrate may also be inserted into a matching socket in the  
35      PC board to form the electrical connection between the  
36      sensing element and the PC board. Alternatively, the entire  
37      back side of the substrate can be adhered to the printed  
38      circuit board surface using an anisotropically conductive  
39      thin film adhesive which has a high conductivity between

1 contacts 74 and 82 and which has a low conductivity resulting  
2 in preferably many times higher resistance between adjoining  
3 contacts than between matching contacts, in practice at least  
4 one hundred times different. An example of such adhesive is  
5 tape NO. 3707 by MMM Corporation, Minneapolis MN. However,  
6 due to the difficulty of applying such material without  
7 trapped air bubbles, it may be preferably to apply adhesive  
8 only to the contacts themselves. In practice a release liner  
9 of polyethylene, mylar or paper with a non-stick surface on  
10 one side is provided on the lower side of the adhesive sheet.  
11 This liner protects the adhesive layer prior to connection of  
12 the disposable multi-element probe to the probe holder and is  
13 removed prior to the connection of the probe to the holder.

14 Preferably, the impedance between contacts 82 and skin  
15 side of the conducting material in the wells should be less  
16 than 100 ohms at 1 kHz and less than 400 ohms at 10 Hz.

17 Impedance between any pair of contacts 82, with the  
18 multi-element probe mounted should preferably be greater than  
19 10 kohm at 1 kHz or 100 kohm at 10 Hz.

20 Another suitable material for producing substrates is  
21 TYVEX (DuPont) substrate which is made from a tough woven  
22 polyolefin material available in various thicknesses and  
23 porosities. If such material having a suitable porosity is  
24 used, contacts 72 and 74 and feed-through 76 can be formed by  
25 a single printing operation with conductive ink on one side  
26 of the TYVEX sheet. Due to the porosity of the TYVEX, the ink  
27 will penetrate to the other side of the TYVEX and form both  
28 contacts and feed-through in one operation.

29 For probe 62 in the embodiment of Fig. 3A, substrate 68  
30 is replaced by a relatively rigid PC board which includes  
31 conducting wires to attach each of electrical contacts 72 to  
32 one of the pins of connector 51 (Fig. 3A) and the rest of the  
33 connecting structure of Fig. 5A may be omitted. It should be  
34 noted that the choice of using the structure of Figs. 3A or  
35 3B (i.e., probes 62 or 62') is an economic one depending on  
36 the cost of manufacture of the probes. While probe 62 is  
37 structurally simpler, the disposable portion of probe 62' is  
38 believed to be less expensive to manufacture in large  
39 quantities. Since it is envisioned that the probes will be

1 used in large quantities and will preferably not be reused,  
2 one or the other may be preferable.

3 The other side of the probe is also protected by a cover  
4 plate 88 (Figs. 5A and 5B) which is attached using any bio-  
5 compatible adhesive to the outer edges of dividers 66 (Fig.  
6 5A) and/or to the hydrogel, which is preferably moderately  
7 tacky. In one preferred embodiment of the invention, the  
8 inner surface of the cover plate 88 is provided with an  
9 electrically conductive layer so that the impedance of each  
10 sensing element from the outer surface of the hydrogel (or  
11 conductive gel) to contact 82, can be measured using an  
12 external source. In addition, if a known impedance is  
13 connected between the conductive layer and a reference point  
14 or a source of voltage, the sensing elements can be tested in  
15 a measurement mode similar to that in which they will finally  
16 be used.

17 Alternatively, a film RC circuit or circuits may be  
18 printed on the inner surface of plate 88 to simulate an  
19 actual impedance imaging situation. Alternatively, plate 88  
20 may be provided with contacts at each sensing location, and  
21 circuitry which may simulate a plurality of actual impedance  
22 imaging situations. Such circuitry may include external or  
23 integral logic such as programmable logic arrays and may be  
24 configurable using an external computer interface. The  
25 simulation may provide a distinct RC circuit for each sensing  
26 element or may provide a sequence of different circuits to  
27 each sensing element to simulate the actual range of  
28 measurements to be performed using the probe.

29 Fig. 5B shows a preferred embodiment of cover sheet 88  
30 (indicated on the drawing as 88') and its mode of attachment  
31 to both the multi-element sensor and the PC board. In this  
32 embodiment a multi-element probe 62" is optionally further  
33 attached to PC board 80 by an adhesive frame 210 which may be  
34 conductive or non-conductive, and which assists in preventing  
35 entry of water or gel under sensor 62". Sensor 62" is  
36 preferably further aligned to PC board 80 by one or more  
37 holes 222 with one or more pins 204, which are permanently  
38 attached to PC board 80 or to a surface adjacent to PC board  
39 80. While pin 204 is shown as being round, using rectangular,

1 triangular, hexagonal pyramidal or other shapes provides  
2 additional alignment of the sensor. In general the upper  
3 portion of the pin should be curved for improved electrical  
4 contact as described below.

5 The upper exposed surface of pin 204 is conductive,  
6 preferably curved and is preferably connected to a signal  
7 reference source by a conductor 202 in PC board 80. Cover  
8 sheet 88' is made of a single integral sheet of easily  
9 deformable polyethylene, Mylar or other suitable plastic.  
10 Cover sheet 88' is preferably removably attached to the upper  
11 side of multi-element probe 62" by a continuous frame of  
12 adhesive 225, which need not be conductive, but which seals  
13 around a lip where cover 88' contacts probe 62" to protect  
14 the quality and sterility of array 230 and to maintain the  
15 moisture content of any medium filling wells 70. Cover 88'  
16 is coated on the side facing probe 62" with a conductive  
17 layer 231, such as any of the various metallic coatings, for  
18 example, aluminum or the thin film coating described above.

19 Cover 88' is preferably formed after conductive coating,  
20 by embossing, vacuforming or other means, to have depressions  
21 233 in the cover located over corresponding wells 70. The  
22 depressions are approximately centered on the center of the  
23 wells and held a small distance " $\delta 1$ " above the surface of  
24 the hydrogel or gel, by means of relatively high sidewalls  
25 226 which are formed at the same time as depressions 233.  
26 Furthermore, the surface of cover 88' preferably has a  
27 concave shape to match the rounded conductive contact surface  
28 of pin 204, from which it is held at a distance " $\delta 2$ ".  
29 Distances  $\delta 1$  and  $\delta 2$  are selected to minimize unintended  
30 physical contact between the conductive inner surface of the  
31 cover, the contacts in the wells and pin 204, for example,  
32 during storage and handling prior to use, which might cause  
33 corrosion over time due to electrochemical processes.

34 Distances  $\delta 1$  and  $\delta 2$  are also preferably selected so that  
35 application of a nominal force (preferably about one  
36 kilogram) against a flat outer surface 232 of cover 88', such  
37 as by a weighted flat plate, will establish contact between  
38 the inner coating 231 and the upper surface of pin 204 and  
39 with the sensing elements or the gel in the wells.

1 By establishing this contact, the conductive inner  
2 surface 231 is connected, on the one hand to signals source  
3 contact 202 and with each sensing element. If the coating is  
4 a conductor, the sensing elements are all excited by the  
5 signal on line 202; if it is a thin film circuit, the contact  
6 is via the thin film circuit. In either event, if line 202 is  
7 excited by a signal, the signal will be transmitted to each  
8 of the sensing elements, either directly, or via a known  
9 impedance.

10 In either case, the multi-element array can be tested by  
11 the system and any residual impedance noted and corrected  
12 when the probe is used for imaging. If the residual impedance  
13 of a given sensing element is out of a predetermined  
14 specification, or is too large to be compensated for, the  
15 multi-element probe will be rejected. Furthermore, the  
16 computer may be so configured that imaging may only take  
17 place after determination of the contact impedance of the  
18 sensing elements or at least of verification that the probe  
19 impedances are within a predetermined specification.

20 While pin 204 is shown as being higher than the top of  
21 the wells, the pin may be at the same height as the wells, or  
22 even below the wells with the cover being shaped to provide a  
23 suitable distance "62" as described above.

24 In an alternative embodiment of the invention, the  
25 contact surface corresponding to pin 204 is printed on or  
26 attached to the surface holding the sensing elements, with  
27 contact to the PC board being via a through contact in  
28 substrate 68, as for the sensing elements.

29 In yet another embodiment of the invention, the  
30 conductive contact surface associated with pin 204 is on the  
31 surface holding the sensing elements adjacent to pin 204. Pin  
32 204 supports this surface and contacts the contact surface  
33 via one, or preferably a plurality of through contacts. Pin  
34 204 is designed to match the contour of the contact surface  
35 and preferably, by such matching, to provide additional  
36 alignment of the probe on the PC board.

37 To avoid drying out of the Gel or other potential  
38 hazards of limited shelf life, the quality of any of the  
39 aforementioned versions of the disposable electrode arrays

1 can be assured by incorporating an identification code,  
2 preferably including manufacturer and serial number  
3 information and date of manufacture. In a preferred  
4 embodiment, the information is coded in a bar code printed on  
5 each disposable probe, which is packaged together with at  
6 least one other such probe (typically 5-50 probes) in the  
7 same packet, which also has the same bar code. A bar code  
8 reader, interfaced with the system computer, reads the  
9 manufacturing information on the packet and each probe,  
10 checking for date and compliance and permitting recording  
11 only for a number of patients equal to the number of probes  
12 in the packet.

13 In a preferred embodiment of the invention a bar code  
14 may be placed on the individual disposable electrode arrays  
15 which can be read by a bar code reader installed in or under  
16 the PC board, for example near reference numeral 83 of Fig.  
17 5B.

18 While the invention has been described in conjunction  
19 with the preferred embodiment thereof, namely a generally  
20 flat, somewhat flexible structure, suitable for general use  
21 and for breast screening, other shapes, such as concave  
22 structures (e.g., brassiere cups) or the like may be  
23 preferable, and in general the shape and configuration of the  
24 detectors will depend on the actual area of the body to be  
25 measured. For example cylindrical arrays can be useful in  
26 certain situations, for example in intra-rectal examinations  
27 of the prostate or colon or inside vessels. In this context,  
28 a probe according to the invention is also useful for  
29 measurements inside the body, for example gynecological  
30 measurements or measurements in the mouth, where the probe is  
31 inserted into a body cavity and contacts the lining of the  
32 cavity, and probes having shapes which correspond either  
33 flexibly or rigidly to the surface being measured can be  
34 used. For example, a multi-element probe in accordance with  
35 the invention may be incorporated into or attached to a  
36 laparoscopic or endoscopic probe.

37 Furthermore, sterilized probes can be used in invasive  
38 procedures in which the probe is placed against tissue  
39 exposed by incision. In this context, the term "skin" or

1 "tissue surface" as used herein includes such cavity lining  
2 or exposed tissue surface.

3 In a preferred embodiment of the invention, PC board 80  
4 and as many elements as possible of probe 62' (or the board  
5 of probe 62) are made of transparent or translucent material,  
6 so as to provide at least some visibility of the underlying  
7 tissue during placement of probe 62. Those elements of the  
8 probe and conductors in the PC board, to the extent that they  
9 are opaque should be made as small as practical to provide  
10 the largest possible view to a technician or clinician to aid  
11 in placement of the probe. Furthermore, probe 62 is slidably  
12 displaceable when used with the above-mentioned conductive  
13 gel to permit moderate lateral adjustment of the probe  
14 position, to aid in placement, to ensure good contact between  
15 each element and the tissue surface to be measured, and to  
16 enable the user to rapidly verify whether detected  
17 abnormalities are artifacts due to poor contact or are  
18 genuine objects, since artifacts remain stationary or  
19 disappear entirely when the probe is moved while genuine  
20 objects just move in a direction opposite to the direction of  
21 movement of the probe.

22 The general shape and size of the multi-element probe  
23 and the size of the conductive sensing elements will depend  
24 on the size of the area to be measured and on the desired  
25 resolution of the measurement. Probe matrix sizes of greater  
26 than 64 x 64 elements are envisioned for viewing large areas  
27 and probes which are as small as 2 x 8 elements can be useful  
28 for measuring small areas. Element size is preferably between  
29 2 mm square and 8 mm square; however, larger sizes and  
30 especially smaller sizes can be useful under certain  
31 circumstances. For the breast probe 62 described above, 24 x  
32 32 to 32 x 40 elements appear to be preferred matrix sizes.

33 Fig. 6A shows a perspective view of a hand held probe  
34 100 in accordance with a preferred embodiment of the  
35 invention. Probe 100 preferably comprises two probe heads, a  
36 larger head 102 and a zoom sensor head 104. A handle 106  
37 connects the sensor heads, houses switching electronics and  
38 provides means for holding and positioning the probes. Handle  
39 106 also optionally incorporates a digital pointing device



1 105 such as a trackball, pressure sensitive button or other  
2 such joystick device. Incorporation of a pointing device on  
3 the probe enables the operator to control the system and  
4 input positional information while keeping both hands on  
5 either the probe or patient. As described below, the digital  
6 pointing device can be used to indicate the position on the  
7 patient's body at which the image is taken.

8 Fig. 6B shows a partially expanded bottom view of probe  
9 100 of Fig. 6A, in accordance with a preferred embodiment of  
10 the invention. Where applicable, like parts of the probes  
11 throughout this disclosure are similarly numbered. Starting  
12 from the bottom of Fig. 6B, the top half of a housing 108A  
13 has a well 110 formed therein. A clear plastic window 112 is  
14 attached to the edge of well 110, and a printed circuit on a  
15 relatively transparent substrate, such as Kapton, designated  
16 by reference 80' (to show its similarity to the corresponding  
17 unprimed element of Fig. 5) is placed on window 112. A  
18 flexible print cable 114 connects the contacts on printed  
19 circuit 62' to acquisition electronics 116. A cable 118  
20 connects the acquisition electronics to the computer. A  
21 second similarly constructed, but much smaller zoom sensor  
22 probe head is attached to the other end of probe 100. Either  
23 of the larger or smaller heads may be used for imaging.

24 A lower half of housing 108B, encloses electronics 116  
25 and print 80', whose face containing a series of contacts  
26 82', is available through an opening 120 formed in the lower  
27 housing half 108B. A mounting frame 122 having two alignment  
28 pins 124 holds print 80' in place. Mounting and connecting  
29 screws or other means have been omitted for simplification.

30 A disposable multi-element probe 62', similar to that of  
31 Fig. 5 is preferably mounted on the mounting frame to  
32 complete the probe.

33 Fig. 7A is a perspective view of a fingertip probe 130  
34 in accordance with a preferred embodiment of the invention as  
35 mounted on the finger 132 of a user. Probe 130 may be  
36 separate from or an integral part of a disposable glove, such  
37 as those normally used for internal examinations or external  
38 palpation. The fingertip probe is especially useful for  
39 localizing malignant tumors or investigating palpable masses

1 during surgery or during internal examinations. For example,  
2 during removal of a tumor, it is sometimes difficult to  
3 determine the exact location or extent of a tumor. With the  
4 local impedance map provided by the fingertip probe 130 and  
5 the simultaneous tactile information about the issue  
6 contacted by the probe, the tumor can be located and its  
7 extent determined during surgery. In a like fashion, palpable  
8 lumps detected during physical breast (or other) examination  
9 can be routinely checked for impedance abnormality.

10 Fig. 7B shows a flexible probe array 140 which is shown  
11 as conforming to a breast being imaged. Probe array 140  
12 comprises a plurality of sensing elements 141 which contact  
13 the tissue surface which are formed on a flexible substrate.  
14 Also formed on the flexible substrate are a plurality of  
15 printed conductors 142 which electrically connect the  
16 individual sensing elements 141 to conductive pads on the  
17 edge of the substrate. A cable connector 144 and cable 145  
18 provide the final connection link from the sensing elements  
19 to a measurement apparatus. Alternatively, the flexible array  
20 may take a concave or convex shape such as a cup (similar in  
21 shape to a bra cup) which fits over and contacts the breast.

22 The flexible substrate is made of any thin inert  
23 flexible plastic or rubber, such as those mentioned above  
24 with respect to Fig. 5A. Array 140 is sufficiently pliant  
25 that, with the assistance of viscous gel or conductive  
26 adhesive, the sensor pads are held in intimate contact with  
27 the skin or other surface, conforming to its shape.

28 Fig. 8 shows an intra-operative paddle type probe 140  
29 used, in a similar manner as probe 130, for determining the  
30 position of an abnormality in accordance with a preferred  
31 embodiment of the invention. This probe generally includes an  
32 integral sensing array 143 on one side of the paddle.  
33 Preferably, the paddle is made of substantially transparent  
34 material so that the physical position of the array may be  
35 determined and compared with the impedance map.

36 Fig. 9 shows a laparoscopic probe 150 in accordance with  
37 a preferred embodiment of the invention. Probe 150 may have a  
38 disposable sensing array 152 mounted on its side or the  
39 sensing array may be integral with probe 150, which is

1 disposable or sterilizable.

2 Multi-element probes, such as those shown in Figs. 7, 8  
3 and 9, are preferably disposable or sterilizable as they are  
4 generally are used inside the patients body in the presence  
5 of body fluids. In such situations, there is generally no  
6 need or desire for a conductive gel in addition to the probes  
7 themselves. Generally, printed sensing elements, such as  
8 those printed with silver-silver chloride ink, or sensing  
9 elements formed of conductive silicone, hydrogel or of a  
10 conductive sponge may be used. While in general it is  
11 desirable that the sensing elements on these multi-element  
12 probes be separated by physical separators 66 (as shown in  
13 Fig. 5), under some circumstances the physical distance  
14 between the elements is sufficient and the separators may be  
15 omitted.

16 When performing a needle biopsy, a physician generally  
17 relies on a number of indicators to guide the needle to the  
18 suspect region of the body. These may include tactile feel,  
19 X-Ray or ultrasound studies or other external indicators.  
20 While such indicators generally give a reasonable probability  
21 that the needle will, in fact take a sample from the correct  
22 place in the body, many clinicians do not rely on needle  
23 biopsies because they may miss the tumor.

24 Fig. 10 shows a biopsy needle 154, in accordance with a  
25 preferred embodiment of the invention, which is used to  
26 improve the accuracy of placement of the needle. Biopsy  
27 needle 154 includes a series of sensing elements 156 spaced  
28 along the length of the probe. Leads (not shown) from each of  
29 these elements bring signals from the elements to a detection  
30 and computing system such as that described below. Elements  
31 156 may be continuous around the circumference, in which case  
32 they indicate which portion of the needle is within the tumor  
33 to be biopsied. Alternatively, the electrodes may be  
34 circumferentially segmented (a lead being provided for each  
35 segment) so that information as to the direction of the tumor  
36 from the needle may be derived when the needle is not within  
37 the tumor. Such an impedance sensing biopsy needle can be  
38 used, under guidance by palpation, ultrasound, x-ray  
39 mammography or other image from other image modalities

1 (preferably including impedance imaging as described herein),  
2 taken during the biopsy or prior to the biopsy to improve the  
3 accuracy of placement of the needle. In particular, the  
4 impedance image from the needle may be combined with the  
5 other images in a display. While this aspect of the invention  
6 has been described using a biopsy needle, this aspect of the  
7 invention is also applicable to positioning of any elongate  
8 object such as an other needle (such as a localizing needle),  
9 an endoscopic probe or a catheter.

10 Returning now to Figs. 1-3 and referring additionally to  
11 Figs. 11-14, a number of applications of multi-element probes  
12 are shown. It should be understood that, while some of these  
13 applications may require probes in accordance with the  
14 invention, others of the applications may also be performed  
15 using other types of impedance probes.

16 Fig. 11A shows the use of the biopsy needle in Fig. 10  
17 together with an optional ultrasound imaging head in  
18 performing a biopsy. A breast 160 having a suspected cyst or  
19 tumor 162 is to be biopsied by needle 154. An ultrasound head  
20 164 images the breast and the ultrasound image, after  
21 processing by an ultrasound processor 166 of standard design  
22 is shown on a video display 168. Of course, the ultrasound  
23 image will show the biopsy needle. The impedance readings  
24 from probe 154 are processed by an impedance processor 170  
25 and are overlaid on the ultrasound image of the biopsy needle  
26 in the display by a video display processor 172.

27 In one display mode, the portions, as shown in Fig. 11B  
28 of the needle which are within the tumor or cyst and which  
29 measure a different impedance from those outside the tumor,  
30 will be shown in a distinctive color to indicate the portion  
31 of the needle within the tumor or cyst. In a second display  
32 mode, the impedance measured will be indicated by a range of  
33 colors. In yet a third embodiment of the invention, in which  
34 circumferentially segmented sensing elements are employed,  
35 the impedance processor will calculate radial direction of  
36 the tumor from the needle and will display this information,  
37 for example, in the form of an arrow on the display.

38 The image sensing biopsy needle can also be used with  
39 one or more imaging arrays (28, 30) such as those shown in

1 Fig. 6 or Fig. 3B to impedance image the region to be  
2 biopsied during the biopsy procedure. Alternatively, at least  
3 one of the arrays can be an imaging array of the non-  
4 impedance type. In one preferred embodiment, shown in Fig.  
5 11C, the needle is inserted through an aperture (or one of a  
6 plurality of apertures) 174 in a multi-element probe which is  
7 imaging the region. The region may, optionally, be  
8 simultaneously viewed from a different angle (for example at  
9 90° from the probe with the aperture) with an other impedance  
10 imaging probe. In the case that both arrays 28 and 30 are  
11 impedance imaging arrays, the biopsy needle or other elongate  
12 object can either have impedance sensing or not, and the two  
13 images help direct it to the region. The probe with one or  
14 more apertures is sterile and preferably disposable. This  
15 biopsy method is shown, very schematically, in Fig. 11C.

16 In an alternative preferred embodiment of the invention,  
17 only the perforated plate through which the needle or  
18 elongate object is passed is an imaging array. In this case  
19 the array through which the needle passes give a two  
20 dimensional placement of the impedance abnormality while an  
21 imaging or non-imaging impedance sensor on the needle gives  
22 an indication of when the needle has reached the region of  
23 impedance abnormality, as described above.

24 Alternative guiding systems for frontal and lateral  
25 breast biopsy or for guiding an elongate element to a desired  
26 impedance region of the body are shown in Figs. 11D and 11E,  
27 respectively.

28 Fig. 11D shows a system for in which two relatively  
29 large plate multi-element probes 28, 30 are placed on  
30 opposite sides of the desired tissue, shown as a breast 160  
31 of a prone patient 161. Sensor array probes 28 and 30 are  
32 held in position by positional controller 181 via rotatable  
33 mounts 191. A mount 198 positions a biopsy needle 199 within  
34 the opening between probe arrays 28 and 30, and is operative  
35 to adjust its height. A suspicious region 183 which is  
36 located at positions 184 and 185 on arrays 28 and 30  
37 respectively as described herein, which information is  
38 supplied to a CPU 197, which determines the position of the  
39 suspicious region for controller 181. The controller then

1 inserts the needle into the suspicious region, for example,  
2 to take the biopsy. Biopsy needle 199 is preferably of the  
3 type shown in Fig. 10 to further aid in positioning of the  
4 needle. As indicated above, this is not required for some  
5 embodiments of the invention.

6 Alternatively, biopsy needle 199 may be inserted through  
7 holes formed between the elements of probes 28 and/or 30 as  
8 described above. Furthermore, while automatic insertion of  
9 the biopsy needle is shown in Fig. 11D, manual insertion and  
10 guidance based on impedance images provided by the probes is  
11 also feasible.

12 Fig. 11E shows a system similar to that of Fig. 11D in  
13 which the imaging and biopsy needle insertion is from the  
14 side of the breast, rather than from the front. Operation of  
15 the method is identical to that of Fig. 11D, except that an  
16 additional probe 29 may be provided for further localization  
17 of suspicious region 183. Alternatively, one or two of the  
18 probes may be substituted by plates of inert material for  
19 holding and positioning the breast.

20 It should be noted that while the breast has been used  
21 for illustrative purposes in Figs. 11A through 11E, the  
22 method described is applicable to other areas of the body,  
23 with necessary changes due to the particular physiology being  
24 imaged.

25 It should be understood that one or more of the elements  
26 on the needle may themselves be electrified to cause them to  
27 "light-up" on the image. This electrification may be AC or DC  
28 may be the same or different from the primary image stimulus,  
29 may have a single frequency or a complex form and may be  
30 applied in a continuous or pulsed mode. If one or more of the  
31 sensing elements is used in this manner, said elements are  
32 preferably alternatively used to apply an electrification  
33 signal and to function as sensors, i.e., to sense signals  
34 from the primary stimulus.

35 Fig. 12 shows, very schematically, the intra-operative  
36 probe of Fig. 8 combined with a video camera 256 to more  
37 effectively correlate the impedance measurement with the  
38 placement of the probe on the body. An intra-operative probe  
39 140 preferably having a number of optically visible fiduciary

1 marks 146 is placed on the suspect lesion or tissue. A video  
2 camera 256 sequentially views the area without the probe and  
3 the same area with the probe in place and displays a  
4 composite image on a video display 258 after processing by a  
5 processor 260. Processor 260 receives the impedance data from  
6 probe 140, determines the positions of the fiduciary marks  
7 from the video image and superimposes the impedance image on  
8 the video image, with or without the probe, which is  
9 displayed on display 258.

10 Fig. 13 shows a laparoscopic or endoscopic probe 250  
11 used in conjunction with a fiber-optic illuminator/imager  
12 252. In this embodiment, the laparoscopic impedance probe,  
13 which is formed on a flexible, preferably extendible paddle,  
14 is viewed by the illuminator/imager which is preferably a  
15 video imager, which is well known in the art. Probe 250 can  
16 be either round or flat, depending on the region to be  
17 imaged. When the imager views a suspicious lesion or tissue,  
18 probe 250 is extended to determine the impedance properties  
19 of the lesion. The combination of probe 250 and imager 252  
20 may be incorporated in a catheter 254 or other invasive  
21 element appropriate to the region of the body being  
22 investigated.

23 Optically visible fiduciary marks 253 on probe 250 are  
24 preferably used to determine the position of probe 250 within  
25 the video image of the tissue seen by fiber-optic  
26 illuminator/imager 252, in a manner similar to that discussed  
27 above with respect to Fig. 12.

28 In a preferred embodiment of a system using any of the  
29 biopsy needle, intra-operative probe, finger tip probe or  
30 other embodiments described above, an audible sound  
31 proportional to an impedance parameter measured by the needle  
32 or other sensor in or on the body is generated by the system  
33 computer. This feature may be useful in situations where the  
34 probe is placed in locations which are difficult to access  
35 visually, such as suspected lesions during surgery. Such an  
36 audible sound could include any kind of sound, such as a tone  
37 whose frequency is proportional to the measured parameter or  
38 similar use of beeps, clicks, musical notes, simulated voice  
39 or the like. This feature can also be used for non-surgical

1 procedures such as rectal, vaginal or oral examinations, or  
2 other examinations.

3 Fig. 16 shows methods useful for estimating the depth  
4 of a lesion and also for determining if a image contains a  
5 true lesion or an artifact.

6 A breast or other region 160 is imaged by a probe 270,  
7 for example, the probe of Figs. 1-3 or Figs. 6A and 6B. The  
8 depth of a local impedance deviation can be estimated by  
9 palpating the breast or other region by a finger 272 or a  
10 plunger 274. The displacement of the local deviation on the  
11 image will be maximized when the palpation is at the same  
12 level as the lesion. It should also be understood that, where  
13 palpation causes movement of the local deviation on the  
14 impedance image, this is an indication that the deviation is  
15 "real" and not an artifact.

16 In a similar manner, application of variable compression  
17 to the imaging probe will result in a variation of the  
18 distance from the probe to deviation under the probe. This  
19 distance variation will cause a corresponding variation in  
20 the size and intensity of the deviation, thus helping to  
21 verify that the deviation is not artifactual.

22 Alternatively or additionally, the probe can be moved  
23 along the surface of the tissue without moving the tissue. In  
24 this case, surface effects will have a tendency to either  
25 disappear or to move with the probe (remain stationary in the  
26 image) while real anomalies will move, on the image, in the  
27 opposite direction from the movement of the probe.

28 Alternatively or additionally, the probe and the tissue  
29 can be moved together without moving the underlying structure  
30 (such as the bones). Tissue lesions will remain relatively  
31 stationary in the image while bone artifacts will move in the  
32 opposite direction.

33 In operation, a system according to the present  
34 invention measures impedance between the individual sensing  
35 elements and some reference point (typically the signal  
36 source point) at some other place on the body. Generally, in  
37 order to produce an interpretable impedance image, the  
38 sensing elements in the multi-element probe should detect  
39 distortions in the electric field lines due solely to the



1 presence of a local impedance difference between embedded  
2 tissue of one type (for example, a tumor) and surrounding  
3 tissue of another type (for example, normal adipose tissue).

4 To avoid distortion in the field lines, the reference  
5 point is typically placed far from the sensor array, all  
6 sensing elements are all at ground or virtual ground, and the  
7 current drawn by the elements is measured. Since the probe is  
8 at ground (an equipotential) the electric field lines (and  
9 the current collected by the elements) are perpendicular to  
10 the surface of the multi-element probe. In principle, if  
11 there are no variations of impedance below the probe, each  
12 element measures the integrated impedance below the element.  
13 This first order assumption is used in the determination of  
14 the position and/or severity of a tumor, cyst or lesion. It  
15 is clear, however, that the multi-element probe covers only a  
16 portion of even the organ which is being imaged. The area  
17 outside the area of the probe is not at ground potential,  
18 causing the field lines to bend out at the periphery of the  
19 probe, biasing the edge of the impedance image.

20 To reduce this effect, a conductive "guard ring" is  
21 provided around the edge of the imaged area to draw in and  
22 straighten the field lines at the edge of the imaged area.  
23 This guard ring, if one is desired, can consist of merely  
24 ignoring the, presumably distorted, currents drawn by the  
25 elements at (or near) the edge of the probe and ignoring the  
26 measurements made by these elements. In general, while the  
27 use of a guard ring reduces the edge effect at the edge of  
28 the field, it is still generally necessary to determine  
29 values for comparison or determination of polychromatic values  
30 near the ring based only on pixels near the ring and not on  
31 the image as a whole.

32 Furthermore, to possibly reduce the baseline impedance  
33 contributed to the local impedance image by tissue between  
34 the remote signal source and the region near the probe, an  
35 additional reference electrode may be placed on the patient's  
36 body relatively near the multi-element probe. For example, if  
37 the source is placed at the arm of the patient and the breast  
38 is imaged from the front, a reference electrode for sensing a  
39 reference voltage can be placed at the front of the shoulder

1 of the patient. The measured impedances are then reduced by  
2 the impedance value of the reference electrode.  
3 Alternatively, the impedance values of the elements of the  
4 multi-element probe are averaged to form a reference  
5 impedance, and the display of the impedance map is corrected  
6 for this reference impedance.

7 One way to substantially avoid at least some of the  
8 above- mentioned problems is to use the apparatus shown in  
9 Figs. 1-3. As indicated above, the apparatus incorporates two  
10 probe heads 28 and 30. The breast to be imaged is placed  
11 between the probe heads and the breast is compressed by the  
12 heads (although generally to a lesser degree than in X-Ray  
13 mammography) so that the breast forms a relatively flat  
14 volume and fills the region between the probes. It should be  
15 noted that, if the current is measured at each of the sensing  
16 elements in both probes, then two somewhat different images  
17 of the same region are generated. Avoidance of the problems  
18 also results when the two multi-element probes are not  
19 parallel as described above.

20 It should be noted that when used on breasts, the images  
21 produced by the pair of large, flat probes of Fig. 3 have the  
22 same geometric configuration as standard mammograms.  
23 Furthermore if used in the same compression orientations, the  
24 impedance images can be directly compared to the  
25 corresponding mammograms. In one preferred embodiment of the  
26 invention, mammograms corresponding to the impedance images  
27 to be taken are digitized, using film scanning or other  
28 digitization means known in the art, and entered into the  
29 system computer. If the mammogram is already digital, such as  
30 may be provided by a digital mammogram, the image file can be  
31 transferred from the mammogram.

32 The mammograms and impedance images can be overlaid or  
33 otherwise combined to form a single image. Such an image  
34 could highlight those areas of the mammogram in which the  
35 impedance is particularly low or high. Such a combined image  
36 thus presents two independent readouts (impedance and  
37 radiographic density) of the same well defined anatomical  
38 region in a known geometric orientation, to facilitate  
39 interpretation, correlation with anatomy and localization.

1 It is well known that the resolution of objects in an  
2 impedance image is reduced with distance of the object from  
3 the probe. Thus, it is possible to estimate the distance of  
4 the object from the two probes based on the relative size of  
5 the same object on the two different probes. As indicated  
6 above, two opposing views of the breast may be taken. This  
7 would provide further localization of the object.

8 In one mode, the sensing elements of one probe are all  
9 electronically floating while the elements of the other probe  
10 are at a virtual ground (inputs to sensing electronics), and  
11 a remote signal source is used, as previously described.  
12 After an image is obtained from the one probe, the roles of  
13 the two probes are reversed to obtain an image from the other  
14 probe.

15 Alternatively, if all of the elements of one of the flat  
16 probes are electrified to the same voltage and the measuring  
17 probe is kept at virtual ground, the currents drawn from and  
18 received by the elements of both probes form a two  
19 dimensional admittance image of the region between the  
20 probes.

21 In a further preferred embodiment of the invention, one  
22 or a few closely spaced sensing elements on one of the probes  
23 is electrified, and the others are left floating. This would  
24 cause a beam-like flow of current from the electrified  
25 elements to the other sensing elements on the other probe.  
26 The object would disturb this flow causing impedance  
27 variations which are strongest for those elements which are  
28 in the path of the current disturbed by the object. If a  
29 number of such measurements are made with, each with a  
30 different group of electrodes being electrified, then good  
31 information regarding the position of the object can be  
32 obtained.

33 In practice, as indicated above, orthogonal views of the  
34 breast are taken giving additional position information.

35 In preferred embodiments of the invention the breast is  
36 imaged at a plurality of frequencies and both the real and  
37 imaginary parts of the impedance are calculated. The  
38 sensitivity of the detection of malignant tissue is a  
39 function of frequency, and, for a particular frequency, is a

1 function of the impedance measure or characteristic used for  
 2 imaging, for example, real part of the impedance (or  
 3 admittance), imaginary part of the impedance (or admittance),  
 4 absolute value of the impedance (or admittance), phase of the  
 5 impedance (or admittance), the capacitance or some function  
 6 of the impedance or of admittance components.

7 In a practical situation, an impedance measure should  
 8 give the maximum contrast between a malignancy and non-  
 9 malignant tissue. It is therefore desirable to determine the  
 10 frequency or combination of frequencies which give maximum  
 11 detectability and to determine it quickly. One method of  
 12 determining the frequency is to perform swept frequency  
 13 measurements and to use the frequency or combination of  
 14 frequencies which results in the best contrast.  
 15 Alternatively, a number of images taken at relatively close  
 16 frequencies can be used. It is believed that for many  
 17 purposes, at least four samples should be taken in the range  
 18 between and including 100 and 400 Hz and, preferably, at  
 19 least one or two additional images are taken at frequencies  
 20 up to 1000 Hz.

21 A second method is to use a pulsed excitation and  
 22 Fourier analysis to determine impedance over a range of  
 23 frequencies. The optimum frequency or frequencies determined  
 24 from the swept or pulsed measurement are then used in a  
 25 single or multiple frequency measurement. A pulse shape which  
 26 has been found useful in this regard is a bi-polar square  
 27 pulse having equal positive and negative going pulses of 5-10  
 28 millisecond duration and fast rise and fall times.

29 A number of measures of the impedance, as described  
 30 below, have been found useful for comparing different areas  
 31 of the image. Generally, it is useful to display a gray scale  
 32 or pseudo-color representation of the values of the impedance  
 33 measure, either on a linear scale or where the square of the  
 34 impedance measure is displayed. Also useful is an "absorption  
 35 scale" where the value of an impedance measure,  $v$ , is  
 36 displayed as:

$$37 \quad d(v) = (max-1) * (exp(v * (max-1) - 1)) / (e-1),$$

38 where max is the maximum normalized value of  $v$ . Generally,  
 39 the display is most useful when the measure is normalized,

1 either by division or subtraction of the minimum or average  
2 value of the measure in the display or the estimated standard  
3 deviation or other measure of variance for the image.

4 Furthermore, the display may be automatically windowed  
5 to include only those values of the impedance measure  
6 actually in the image, or to include a relative window of  
7 selectable size about the average value of the impedance  
8 measure. The range of values to be displayed may also be  
9 determined using a baseline average value measured at a  
10 region remote from irregularities, i.e., remote from the  
11 nipple of the breast. Alternatively, the baseline average may  
12 be a predetermined average value as measured for a large  
13 group of patients. Alternatively, a reference region on the  
14 image may be chosen by the user to determine the baseline  
15 average to be used for windowing.

16 While the display may show the exact measure for each  
17 pixel as is conventional, for example, in displays of nuclear  
18 medicine images, in a preferred embodiment of the invention  
19 the display is an interpolated image formed by quadratic or  
20 cubic spline interpolation of the impedance measure values.  
21 This type of display removes the annoying checkerboard effect  
22 of the relatively low resolution impedance image without any  
23 substantial loss of spatial or contrast detail.

24 The measures of impedance which have been found useful  
25 for comparing different areas of the image may be grouped as  
26 single frequency measures and polychromic measures.

27 Single frequency measures include the admittance,  
28 capacitance, conductance and phase of the admittance and its  
29 tangent. These measures may be measured at some predetermined  
30 frequency, at which the sensitivity is generally high, or at  
31 a frequency of high sensitivity determined by a preliminary  
32 swept or pulsed measurement. Cancer typically has  
33 significantly higher phase than the average surrounding  
34 tissue, with greatest difference at low frequencies such as  
35 100 Hz, but often significant up to 5 KHz.

36 Polychromic impedance measures are based on measurements  
37 at more than one frequency, such as on a spectral curve based  
38 on fitting a set of capacitance (C) and conductance (G)  
39 values determined at a plurality of frequencies using linear

1 interpolation, quadratic interpolation, cubic spline, band  
2 limited Fourier coefficients, or other methods known in the  
3 art.

4 One polychromic measure is a spectral width measure. For  
5 a given pixel or region of interest the value of C parameter  
6 falls (and the G parameter rises) with frequency. The  
7 spectral width of the spectrum is the width to a given  
8 percentage fall in the C value as compared to the value at  
9 some low frequency, for example 100 Hz. If the parameter does  
10 not fall by the given percentage in the measured range it is  
11 assigned an impedance measure equal to the full measured  
12 bandwidth. Similarly, the spectral width of the G-spectrum is  
13 the width to a given rise in the G-Parameter compared to the  
14 value at some low frequency, for example 100 Hz, or  
15 alternatively, the fall in G with decreasing frequency  
16 compared to the value at some high frequency, for example  
17 3000 Hz.

18 A second polychromic measure is a spectral quotient in  
19 which the impedance measure is the ratio of the measured  
20 value of G or C parameters at two preset frequencies, which  
21 may be user selected, or which may be selected based on the  
22 swept or pulsed measurements described above. This measure,  
23 as all of the others may be displayed on a per-pixel basis or  
24 on the basis of a region of interest of pixels, chosen by the  
25 user.

26 A third type of polychromic measure is based on a  
27 Relative Difference Spectrum determination. In this measure,  
28 the capacitance or conductance for a given region of interest  
29 (or single pixel) is compared to that of a reference region  
30 over the spectrum to determine a numerical difference between  
31 the two as a function of frequency. The thus derived Relative  
32 Difference Spectrum is then analyzed. For example, a spectral  
33 width measure as described above has been found to be a  
34 useful measure of abnormalities. Normally the width is  
35 measured where the relative difference spectrum passes from  
36 positive to negative, i.e., where the C or G is equal to that  
37 of the reference region. For capacitance, this spectrum width  
38 is designated herein as the Frequency of Capacitance  
39 Crossover (FCX). This measure has been found to be especially

1 useful in classification of tissue types as described below.

2 A fourth type of polychromic measure is based on a  
3 Relative Ratio Spectrum determination. This is similar to the  
4 Relative Difference Spectrum, except that the ratio of the  
5 values between the reference area and the region of interest  
6 is used. A spectral width measure can be determined for this  
7 spectrum in the same manner as for the Relative difference  
8 Spectrum. Normally, the width is measured where the ratio is  
9 1. This width is the same as the width of Relative Difference  
10 Spectrum at the zero (cross-over) point.

11 A fifth type of polychromic measures are the Positive  
12 and Negative Integrated Relative Difference for Capacitance  
13 and/or Conductance abbreviated C (for capacitance) or G (for  
14 conductance) NIRD or PIRD. These values are calculated by  
15 adding up the negative (or positive) deviations of the  
16 capacitance (or conductance) values in the area of  
17 abnormality from those of a representative value (or range of  
18 values) of the capacitance (or conductance) at the various  
19 measured frequencies. This representative value or range is  
20 determined from pixel values in the image selected to exclude  
21 exceptionally high or low capacitance (or conductance)  
22 values. The same pixel may have both a C-NIRD and a C-PIRD if  
23 its capacitance deviates positively from the representative  
24 value for some subset of the frequencies and negatively from  
25 the representative value for a different subset of the  
26 frequencies. The C-NIRD, C-PIRD and G-NIRD measures have been  
27 found to be especially useful for characterizing tissue type  
28 as described below.

29 A sixth polychromic measure is the integrated phase. For  
30 a given pixel in the image, the phase is measured at a  
31 plurality of frequencies in a desired frequency range,  
32 typically 100 to 5000 Hz. The integrated phase is the sum of  
33 the phase over a number of frequencies, typically about 13  
34 frequencies between 100 and 3200 Hz. Alternatively,  
35 integration may be performed using the trapezoidal rule or by  
36 integrating another functional fit to the sampled values in  
37 the desired frequency range. Cancer typically has  
38 significantly higher integrated phase. The integrated tangent  
39 of the phase is an alternative measure of this measure.

1       A seventh polychromic measure is the integrated phase  
2 difference. In a given image, the phase of each pixel is  
3 measured at each of a plurality of frequencies in a desired  
4 frequency range, typically 100 to 5,000 Hz and the median or  
5 average phase determined for the image at each frequency. In  
6 calculating the median or the average, the highest and lowest  
7 values are preferably excluded by using such methods as (1)  
8 including only pixels whose values lie within a specified  
9 range of the pixel histogram, such as only those between the  
10 25 and 75 percentile phase values for the image. For each  
11 frequency, the median or average for the image is subtracted  
12 from the phase value for each pixel. This results in a phase  
13 difference spectrum which is positive for frequencies where  
14 the pixel value is higher than average and negative where it  
15 is lower. The sum of the phase differences is the integrated  
16 phase difference (IPD), and the sum of all the positive phase  
17 differences is the integrated positive phase difference. Both  
18 these measures are significantly higher for cancer than for  
19 normal surrounding tissues.

20       An eighth polychromic measure is the specific frequency.  
21 The phase of each pixel is measured at each of a plurality of  
22 frequencies in a desired frequency range, typically 100 to  
23 5000 Hz. The resultant spectrum is fitted to a piecewise  
24 linear function, a spline function or a functional fit as  
25 known in the art. The lowest frequency at which the phase  
26 reaches 45 degrees is defined as the Specific Frequency.  
27 Specific Frequency is typically lower for cancer (range of  
28 100 to 800 Hz) than for normal surrounding tissue (range of  
29 1200 Hz to several kilohertz. The RC time constant evaluated  
30 at the specific frequency is also a useful related  
31 polychromic measure, being lower for cancer.

32       A ninth polychromic measure is the capacitance spectral  
33 slope, i.e., the derivative of the capacitance curve (or of  
34 the log capacitance curve). as a function of frequency,  
35 evaluated at a given frequency. This is considered to be a  
36 polychromic measure, since its determination requires the  
37 measurement of the capacitance at more than one point.  
38 Capacitance Spectral slope in the range 100 to 5000 Hz is  
39 typically negative and typically has a higher absolute value



1 in cancer vs. normal pixels, particularly at low frequencies  
2 such as 100 to 500 Hz.

3 A tenth polychromic measure is the conductance spectral  
4 slope, the derivative of the conductance (or of the log  
5 conductance) evaluated at a given frequency. Conductance  
6 Spectral slope in the range 100 to 5000 Hz is typically  
7 positive and typically has a lower value in cancer vs. normal  
8 pixels, particularly at low frequencies such as 100 to 500  
9 Hz.

10 The NIRD and PIRD measures may be defined in various  
11 ways. For example, the deviations from the representative  
12 value may be used in the calculation only when they exceed  
13 some minimum value. The deviation may be expressed as a the  
14 actual numerical deviation or more preferably as a ratio or  
15 as a deviation normalized to some "standard" deviation of the  
16 capacitance or conductance which is characteristic of normal  
17 tissue, as defined below.

18 Preferably, the value representative of normal tissue is  
19 derived by looking at pixel values representative of some  
20 proportion of the total number of pixels in an image. For  
21 example if a 8x8 image were used, and the anomalous portion  
22 occupied less than 25% of the image, the 16 pixels having  
23 each of the highest and the lowest values would not be  
24 considered. The representative value would then be, for  
25 example, the mean value of capacitance or conductance of the  
26 remaining pixels and a standard deviation would be the range  
27 of pixel values among the 32 pixels which are considered.

28 This determination is based on the practical  
29 consideration that almost always at least 50% of the pixels  
30 represent normal tissue. It is clear that many other measures  
31 of the representative value and of the "standard" deviation  
32 will be equally useful in the practice of the invention and  
33 that such measures may be computed in many different ways.  
34 Furthermore the range of pixels which are considered "normal"  
35 may be adjusted depending on the type of tissue actually  
36 being measured. For example, for tissue having large areas  
37 with apparently high values, a range of pixel values such as,  
38 for example 20%-50% (instead of the 25%-75% described above)  
39 may be more useful.

1 Another potentially useful polychromic parameter is the  
2 slope of the logarithm of the capacitance of a given pixel or  
3 region as a function of frequency. This curve generally has a  
4 shape which is predominantly linear. Alternatively, the ratio  
5 of the slope of the capacitance of the particular pixel to  
6 the slope of the capacitive representative value may be  
7 useful.

8 Furthermore, it may be useful to consider, as an  
9 additional polychromic measure, the maximum of one of the  
10 other polychromic measures, for example, the capacitance,  
11 conductance, Relative Difference Spectrum, Relative Ratio  
12 Spectrum, etc.

13 In general, some pixels are excluded from the  
14 characterization. These would include "No-Contact" pixels  
15 having near zero conductance and capacitance values and  
16 "Contact Artifactual Hot Spots" which are pixels, with  
17 elevated capacitance or conductance values, next to no  
18 contact pixels.

19 In impedance measurements of the breast in both men and  
20 women, normal breast tissue has a low capacitance and  
21 conductivity, except in the nipples, which have a higher C  
22 and G values than the surrounding tissue with the maximum  
23 obtained at the lowest frequency recorded, typically 100 Hz.  
24 The nipple capacitance and conductance remains very much  
25 higher than the surrounding tissue up to about 1400 Hz for  
26 fertile patients and up to about 2500 Hz for older patients  
27 (which is reduced to 1400 Hz for older patients by estrogen  
28 replacement therapy). These frequencies represent the normal  
29 range of spectral widths for the Relative and Difference  
30 Spectra. Tumors can be recognized by very high C and G  
31 relative ratio or relative difference values at all  
32 frequencies below 1000 Hz and moderate difference or ratio  
33 values for frequencies up to 2500 Hz or even higher.

34 Capacitance and conductance values are measured by  
35 comparing the amplitude and phase of the signal received by  
36 the sensing elements. Knowing both of these measures at the  
37 same points is useful to proper clinical interpretation. For  
38 example, as illustrated below in Fig. 14, a region of  
39 elevated conductivity and reduced capacitance (especially at

1 relatively low frequencies, most preferably less than 500 Hz,  
 2 by generally below 2500 Hz and also below 10 kHz) is  
 3 associated with benign, but typically pre-cancerous atypical  
 4 hyperplasia while, as shown in Fig. 15, cancer typically has  
 5 both elevated capacitance and conductivity over, generally, a  
 6 wide frequency range, as compared to the surrounding tissue.  
 7 Proper differential diagnosis is aided by having the  
 8 frequency samples be close enough together so that changes in  
 9 the conductivity and capacitance in the low frequency range  
 10 can be tracked. This also requires the display of both  
 11 capacitance and conductance or the use of an impedance  
 12 measure which is based on an appropriate combination of the  
 13 two.

14 Methods for calculating C and G are given in the  
 15 abovementioned US patents 4,291,708 and 4,458,694, the  
 16 disclosures of which are incorporated herein by reference. A  
 17 preferred embodiment of the invention takes advantage of the  
 18 calibration capability inherent in the use of cover plates as  
 19 shown in Figs. 5A and 5B. It can be shown that if the  
 20 received waveform is sampled at a fixed spacing,  $\delta$ , such  
 21 that N samples are taken in each cycle, then the real and  
 22 imaginary values of the impedance can be determined as:

$$23 \quad G = \Sigma(g_n(V_{(n+\frac{1}{2}N)} - V_n),$$

24 and

$$26 \quad \omega C = \Sigma(c_n(V_{(n+\frac{1}{2}N)} - V_n),$$

27 where  $g_n$  and  $c_n$  are constants determined by a calibration  
 28 procedure and  $V_n$  is the voltage measured at the nth sampling  
 29 point (out of N). The first sample is taken at zero phase of  
 30 the reference signal.

31 One relatively easy way to determine the constants is to  
 32 perform a series of measurements when cover plate is in  
 33 contact with the sensing elements as described above and a  
 34 known impedance is placed between the transmitter and the  
 35 cover plate. Since N coefficients are required for  
 36 determining  $g_n$  and  $c_n$  for each frequency, N values of  
 37 admittance and N measurements are required. For example, if  
 38  $N=4$  (four samples per cycle) four different measurements are  
 39 taken and the sampled signal values are entered into the

1 above equations to give N equations, which are then solved  
2 for the values of the coefficients. The higher the number of  
3 samples, the greater the accuracy and noise immunity of the  
4 system, however, the calibration and computation times are  
5 increased.

6 Alternatively, fewer samples are taken and values for a  
7 number of measurements are averaged, both in the calibration  
8 and clinical measurements to reduce the effects of noise.

9 Artifactual abnormalities in the impedance image can be  
10 caused by such factors as poor surface contact or  
11 insufficient conductive coupling on some or all of the  
12 sensing elements, the presence of air bubbles trapped between  
13 probe and tissue and normal anatomical features such as bone  
14 or nipple.

15 Bubbles can be recognized by their typically lower C and  
16 G values compared to background, often immediately surrounded  
17 by pixels with much higher C and G. Bubbles can be verified  
18 and eliminated by removing the probe from the skin and  
19 repositioning it, and or by applying additional conductive  
20 coupling agent. Contact artifacts can be determined and  
21 accounted for in real time by translating the probe and  
22 viewing the image as described above. Artifacts either  
23 disappear or remain fixed with respect to the pixels, while  
24 real tissue features move, on the image, in a direction  
25 opposite from the motion of the probe. Additionally, as  
26 described above, if the tissue beneath the skin is physically  
27 moved, while the probe and skeletal structure is kept fixed,  
28 only real tissue features will move. If the feature remains  
29 static, it is either a skin feature or bone.

30 If as described above, the probe and the tissue are  
31 moved together without moving the underlying structure (such  
32 as the bones). Tissue lesions and surface effects will remain  
33 relatively stationary in the image while bone artifacts will  
34 move in the opposite direction, thus distinguishing them from  
35 other impedance deviations.

36 Fig. 14 shows one example of a display, according to a  
37 preferred embodiment of the invention. In this display,  
38 capacitance and conductivity images at two positions on a  
39 breast are shown, together with an indication of the

1 positions on the breast at which these images were acquired.

2 In particular, as seen in Fig. 15, the display includes  
3 the capability of displaying up to five sets of capacitance  
4 and conductance images in the five sets of smaller squares.  
5 These images are associated with probe areas indicated as  
6 numbers 1-5 on the breast image shown in the display. In  
7 practice, the examiner manipulates a joystick or other  
8 digital pointing device, such as device 105 shown in Fig. 6A.  
9 This device is manipulated until a square is appropriately  
10 placed on the breast image. The examiner then presses a  
11 button which causes a pair of impedance images to be stored  
12 and displayed on the screen in an appropriate square, and the  
13 indicated position to be displayed on the physiological  
14 (breast) drawing. The small images are numbered from left to  
15 right. Preferably, the examiner can scale the physiological  
16 image so that the dimensions of the breast shown and the  
17 extent of the probe array are compatible. It should be  
18 understood that during the placement of the probe, real time  
19 images (acquired about once every 50-80 msec) of the  
20 capacitance and the conductance are shown, for example in the  
21 large squares to the left of the display.

22 Fig. 14, which represents an actual imaging situation  
23 shows, in the leftmost of the small images, a situation in  
24 which a small atypical hyperplasia which was previously  
25 detected by other means. This position shows an elevated  
26 conductivity and a very slightly reduced capacitance. In  
27 position 2, which is also shown in the two large squares to  
28 the right of the display, a previously unsuspected area  
29 having a capacitance/conductance profile characteristic of  
30 atypical hyperplasia is detected.

31 Fig. 15 shows a study typical of multiple suspected  
32 sites of carcinoma (in positions 2 and 4). The images of  
33 position 4 are shown in enlarged format at the left of the  
34 image. In these sites, both the capacitance and conductance  
35 are elevated with respect to their surroundings.

36 Alternatively, a composite image such as the image of  
37 the sum of the capacitance and conductance images, their  
38 product, their sum or their ratio can be displayed to give a  
39 similar indication of the type of detected anomaly. A color

1 coded composite image can also be displayed, where, for  
2 example, the median value for each image would be black and  
3 where positive and negative values would have a particular  
4 color which, when combined would result in distinctive colors  
5 for suspect impedance deviations.

6         The display shown in Figs. 14 and 15 can be  
7 utilized to show a plurality of images of the same region at  
8 a plurality of frequencies. Alternatively or additionally,  
9 the display can be utilized to show a plurality of different  
10 polychromic measures of the same region. In addition, using,  
11 for example, the fact, as described below with an example,  
12 that a plurality of such measures can be useful in  
13 identifying tissue type more accurately than can a single  
14 measure, the display may include, inter alia, an image in  
15 which portions of the image is identified by tissue type. For  
16 such an image, for example, the color of portions of the map  
17 could represent the type of tissue and the brightness the  
18 certainty of the identification. The type identification and  
19 certainty would depend on the probability that a particular  
20 "mix" of values of the polychromic measures are associated  
21 with a particular tissue type and that not all measures are  
22 always within the specified range for any particular tissue  
23 type. In conjunction with the display of such a map the  
24 individual polychromic measures may be displayed either  
25 together or in sequence to make the determination of the  
26 tissue type more certain.

27         One type of display of multiple polychromic images is to  
28 use a pseudo color image of two or three colors, each of  
29 which represents one of the measures. When a measure for a  
30 portion of the image meets the criteria for a given tissue  
31 type it is displayed in its assigned color. When two or more  
32 such criteria are met a different color is displayed,  
33 depending on which of the criteria are met.

34         Another type of display shows the values of the measures  
35 as iso-contours of varying brightness of a color assigned to  
36 the measure. The conjunction of isocontour lines  
37 characteristic of a given tissue type may then be recognized  
38 from isocontours.

39         Alternatively or additionally, the image can be a pseudo

1 3-D image wherein each of the measures is delineated as a  
2 wire screen of a given color. This allows for the  
3 visualization of more than one measure at the same time.

4 Alternatively, a map of immitance, or the real or  
5 imaginary part thereof is overlaid with indications, based on  
6 polychromic measures of the tissue type involved, as for  
7 example by color coding, by arrows with associated legends or  
8 by other means to alert the operator to suspected sites of  
9 tissue of specific types. Such measures may be calculated  
10 automatically or in response to a query from the operator in  
11 respect to an area of the image of which he is suspicious.

12 It has been found that certain immitance measures and  
13 combinations of measures are characteristic of certain types  
14 of normal and abnormal tissue. In one example of the method  
15 four of the polychromic measures described above can be  
16 utilized separately or, more particularly, in combination to  
17 indicate the presence of certain normal or abnormal tissue.  
18 These four measures are CFX, G-PIRD, C-PIRD and C-NIRD  
19 measure. Other combinations of polychromic measures are also  
20 useful in indicating tissue type.

21 It has been found that normal tissue, as expected, has  
22 low or zero values of all of the measures. Nipples and the  
23 infra-mammary ridge have a very high value of G-PIRD and C-  
24 PIRD together with zero to low value of CFX and no G-NIRD.  
25 Ribs and the costo-chondral junction have low values of C-  
26 PIRD and CFX, moderate to high values of G-PIRD and low  
27 values of C-NIRD. Typical benign hyperplasia has a moderate  
28 to high value of C-NIRD and G-PIRD, a high value of CFX and  
29 no C-PIRD, while precancerous atypical hyperplasia has values  
30 in a range similar to that of typical hyperplasia for C-NIRD,  
31 and G-PIRD but has a moderate value of CFX and C-PIRD. This  
32 allows precancerous atypical hyperplasia to be differentiated  
33 from benign hyperplasia. Furthermore, cancerous tumors appear  
34 to be characterized by medium to high values of C-PIRD and  
35 CFX, high values of G-PIRD and low values C-NIRD. Some  
36 tumors, especially those with very high C-PIRD have no C-  
37 NIRD.

38 The four measures, C-PIRD, C-NIRD, G-PIRD and CFX, form  
39 a four dimensional space in which each set of measurements in

1 designated by a single point. In order to represent such a  
2 space on paper two orthogonal projections of the four  
3 dimensional space are required. One such set of orthogonal  
4 projections is shown in Figs. 18A and 18B. While these  
5 projections fully describe all four measures, they plot the  
6 measures in pairs only. Presenting the regions of the space  
7 which are characterized by the various tissue types in a  
8 single drawing is possible since all of the measures have  
9 only positive (or zero) values. Since only positive values of  
10 the measures are allowed it is possible to combine these two  
11 orthogonal projections, as in Fig. 18C, into a single  
12 projection in which each of the axes represents a positive  
13 value of one of the measures. Fig. 18C shows the information  
14 in a redundant manner (i.e., it actually shows two orthogonal  
15 projections), however, it is useful since it shows all  
16 combinations of the various measures on a single figure.

17 It will be noted from Figs. 18A-C and from the above  
18 discussion that there is some overlap between nipples (and  
19 Infra-mammary ridge) and tumors and also between ribs (and  
20 costo-chondral junction) and tumors. Where ambiguity does  
21 exist (i.e., in the relatively small overlap areas shown in  
22 Fig. 18C) the distinction can generally be made based on the  
23 anatomy of the portion of the patient being imaged. Thus, an  
24 ambiguous tumor/nipple far from the nipple would be  
25 classified as a tumor and a tumor/rib far from the ribs would  
26 be classified as a tumor. Where the anatomy does not allow  
27 for a clear determination, such as for example a tumor which  
28 is close to the nipple, an additional view and/or a different  
29 breast position, palpation or other methods of separating the  
30 anomaly from the normal tissue will generally remove the  
31 ambiguity.

32 While a particular impedance imaging system has been  
33 described as the basis for determining the type of tissue  
34 underlying the anomalies (and causing them) The method is  
35 also believed to be generally useful in tissue type  
36 determination using other types of impedance imaging systems  
37 and also in situations where no image is generated.

38 For example, the method is also potentially useful to  
39 determine tissue types in situations where either a single



1 impedance probe is used or where the image is small and only  
2 anomalous areas are imaged. In these cases the comparison for  
3 determining the measures is made between the values of  
4 capacitance or conductance measured for the anomalous region  
5 as compared to the capacitance or conductance measured for a  
6 nearby region known to be normal.

7 The method is also useful for determining the type of  
8 tissue which is pierced by a biopsy needle or contacted  
9 directly by a probe such as the finger probe of Fig. 7A of  
10 the invasive probes of Figs. 8-10. In these cases a  
11 comparison may be made between values at the tissue to be  
12 characterized and other "normal" tissue.

13 Figs. 17A and 17B show a block diagram of a preferred  
14 embodiment of a system 200 which incorporates a number of  
15 multi-element probes. It should be understood that the exact  
16 design of system for impedance imaging will depend on the  
17 types of probes attached to the system and the exact imaging  
18 modalities (as described above) which are used.

19 As shown in Figs. 17A and 17B the preferred system can  
20 incorporate biopsy needle probe 154, two plate probes 28, 30  
21 such as those shown in Figs. 1-3, scan zoom probe 100 such as  
22 that shown in Fig. 6A, conformal probe 139 such as that shown  
23 in Fig. 7B, a bra-cup probe, finger/glove probe 130 such as  
24 that shown in Fig. 7A, laparoscopic probe 150 such as that  
25 shown in Fig. 9 or an intra-operative probe 140 as shown in  
26 Fig. 8. Furthermore, when three probes are used as in Fig.  
27 11E, provision is made for attachment of a third plate probe.  
28 The position of the plate and needle probes is controlled by  
29 controller 181 as described in respect to Fig. 11D.

30 The probes as connected via a series of connectors,  
31 indicated by reference numeral 302 to a selection switch 304  
32 which chooses one or more of the probes in response to a  
33 command from a DSP processor 306. Selection switch 304  
34 switches the outputs of the probes, namely the signals  
35 detected at the sensing elements of the probes (or amplified  
36 versions of these signals) to a set of 64 amplifiers 308, one  
37 amplifier being provided for each sensing element. For those  
38 probes, such as the large plate probes, which have more than  
39 64 sensing elements, the selection switch will (1)  
- 48 -

1 sequentially switch groups of 64 sensing elements to  
2 amplifier set 308, (2) choose a subset of sensing elements on  
3 a coarser grid than the actual array by skipping some  
4 elements, as for example every second element, (3) sum  
5 signals from adjacent elements to give a new element array of  
6 lower resolution and/or (4) choose only a portion of the  
7 probe for measurement or viewing. All of these switching  
8 activities and decisions are communicated to the switch by  
9 DSP processor 306 which acts on command from a CPU 312. The  
10 output of the amplifiers is passed to a multiplexer 307 where  
11 the signals are serialized prior to conversion to digital  
12 form by a, preferably 12-bit, A/D convertor 310. A  
13 programmable gain amplifier 309, preferably providing a gain  
14 which is dependent on the amplitude of the signals, is  
15 optionally provided to match the signal to the range of the  
16 A/D convertor. The output of A/D 310 is sent to the DSP for  
17 processing as described above. In a preferred embodiment of  
18 the invention DSP 306 is based on a Motorola MC 68332  
19 microprocessor.

20 While 64 amplifiers has been chosen for convenience and  
21 lower cost, any number of amplifiers can be used.

22 The DSP calculates the impedance results and send the  
23 results to CPU 312 for display on a graphic data display 16,  
24 printing on a printer 18 or other output signals generation  
25 as described above by a light indicator 314 or a sound  
26 indicator 316.

27 Alternatively, the DSP directs signal sampling and  
28 averages together the samples or pre-processes them, sending  
29 the averaged or pre-processed samples to CPU 312, which then  
30 performs the impedance calculations.

31 The CPU may also receive images from video camera 256,  
32 for example, when used with an intra-operative probe, from an  
33 endoscopic optics and camera system 320, for example when  
34 the camera views the outer surface of the laparoscopic probe  
35 or from an ultra sound imager 322, for example, in biopsy  
36 performance as shown in Figs. 11A and 11B. When an image is  
37 acquired from one of these cameras a frame grabber 324 is  
38 preferably provided for buffering the camera from the CPU. As  
39 described above, the CPU combines these images with the

1 impedance images provided by one or more probes for display  
2 or other indication to the operator.

3 Fig. 15 also shows a programmable reference signal  
4 generator 326 which receives control and timing signals from  
5 the DSP. The reference signal generator generates excitation  
6 signals which are generally supplied, during impedance  
7 imaging, to reference probe 13, which, as described above, is  
8 placed at a point (or at more than one point) on the body  
9 remote from the region of impedance measurement. Signal  
10 generator 312 may produce a sinusoidal waveform, pulses or  
11 spikes of various shapes (including a bipolar square shape)  
12 or complex polychromatic waveforms combining desired excitation  
13 frequencies. Appropriate impedance calculations, in DSP 306  
14 or in CPU 312, are implemented in accordance with the  
15 waveform of the excitation.

16 Where a breast is imaged and one of the two plates is  
17 used as the source of excitation, as described above, the  
18 output of signal generator is sent to the exciting plate  
19 (signal paths not shown for simplicity). A current overload  
20 sensor 330 is preferably provided after the signal generator  
21 to avoid overloads caused by short circuits between the  
22 reference probe and the imaging probe or ground.

23 Also shown on Fig. 17A is an internal calibration  
24 reference 332 which is preferably used for internal  
25 calibration of the system and for testing and calibration of  
26 the probes.

27 For internal testing and calibration, calibration  
28 reference 232 receives the signals generated by the  
29 programmable reference signals generator as passed to the  
30 selection switch, in series with an internal admittance in  
31 the calibration reference, as selected by the DSP processor.  
32 The DSP processor computes the admittance from signals  
33 received from the A/D convertor and compares the computed  
34 admittance with the actual admittance provided by internal  
35 calibration reference 332. This comparison can be provide an  
36 indication that the system requires adjustment or repair or  
37 can be used to calibrate the system.

38 Similarly, the output of calibration reference 332 may  
39 be provided to probe cover 88 for calibration and quality

1 assurance of a plate or scan probe as described above. Under  
2 this situation, the DSP instructs selection switch 304 to  
3 choose the input from the respective probe.

4 Also provided is a user interface 334 such as a  
5 keyboard, mouse, joystick or combinations thereof, to allow  
6 the operator to enter positional information via the screen  
7 and to choose from among the probes provided and from the  
8 many options of calculation, display, etc.

9 Although described together as the preferred embodiment  
10 of the invention, it is not necessary to use the probes of  
11 the invention, the methods of calculation of impedance and  
12 impedance characteristics of the invention and the preferred  
13 apparatus of the invention together. While it is presently  
14 preferred that they be used together they may each be used  
15 with probes, calculation methods and apparatus for impedance  
16 imaging as applicable and as available.

17 Certain aspects of the invention have been described  
18 with respect to a biopsy needle or with respect to placement  
19 of such a needle. It should be understood that such  
20 description and aspects of the invention are equally  
21 applicable to positioning needles, catheters, endoscopes,  
22 etc.

23 Although various embodiments, forms and modifications  
24 have been shown, described and illustrated above in some  
25 detail in accordance with the invention, it will be  
26 understood that the descriptions and illustrations are by way  
27 of example, and that the invention is not limited thereto but  
28 encompasses all variations, combinations and alternatives  
29 falling within the scope of the claims which follow:

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